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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,729	03/15/2004	Peter N. Kao	STAN-352	1829

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,729	KAO ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/15/04 and tele. interview on 11/06/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *11,14-18 and 25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,13,19-24 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-24 and 30-39, drawn to a method of treating a lung proliferative vascular disorder comprising administering HMG-CoA reductase inhibitor.

II. Claims 25-29, drawn to a method of preventing vascular occlusion in a patient predisposed to developing pulmonary hypertension, comprising administering an antiproliferative agent.

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions have different effects.

Search of Invention I does not reveal the subject matter of the Invention II since the treatment patient group in Invention II is not necessarily suffering or having lung proliferative vascular disorder, namely pulmonary hypertension. Each of the above inventions II and III is drawn to the treatment of totally different conditions and would appear to seek results that differ depending on what diseases or conditions is being treated.

One practicing the invention of any of the above groups would not necessarily be required to practice any of the others. Further a reference which anticipates the invention of one of the above groups would neither anticipate or make obvious any of the other inventions. The search for above inventions would not be co-extensive, particularly as to the literature search required. Clearly each of the above inventions is capable of supporting it's own patent.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

2. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, for example (i) simvastatin from HMG-CoA reductase or antiproliferative agent and (ii) prostanoid from the vasodilator or the additional active agent, under the instant claims of the elected Group. Moreover, whatever specific compound is ultimately elected, applicants are required to list all claims readable thereon.

With the election of a specific exemplified compound, a generic concept will be identified by the examiner as the inventive group for examination.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. During a telephone conversation with Pamela Sherwood on November 06, 2006 a provisional election was made with traverse to prosecute the invention of Group I Invention along with simvastatin and prostanoid as the elected species. Affirmation of this election must be made by applicant in replying to this Office action.

5. Claims 1-10, 12-13, 19-24 and 30-39 read on the elected invention. Claims 11, 14-18 and 25-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-10, 12-13 and 19-24 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for treatment of the specific lung proliferative vascular disorder (e.g., pulmonary hypertension, Eisenmenger's syndrome, pulmonary fibrosis, obliterative bronchiolitis and lymphangioleiomyomatosis) with HMG-CoA reductase inhibitor alone or in combination with the specific additional active agent (e.g., anticoagulants, vasodilators, macrolide anti-inflammatory agents...), does not reasonably provide enablement for "treating a lung proliferative vascular disorder", "chronic thromboembolic disease", "an antiproliferative agent" or "an additional active agent". The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present invention is drawn to a method of treating a lung proliferative vascular disorder, namely pulmonary hypertension, comprising administering an HMG-CoA reductase inhibitor as antiprolifeative agent alone or in combination with additional active agent selected from the group consisting of anticoagulants, vasodilators, macrolide anti-inflammatory agents, diterpenoid triepoxides, endothelin receptor antagonist, geranyl transferase inhibitors, farnesyl transfers inhibitors, and inhibitors of EGF tyrosine kinase, and pharmaceutical acceptable salts and esters thereof.

The specification defines the term "lung proliferative vascular disorder" as "any of the proliferative and oliterative vascular disorders affecting the lung" including "primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, chronic thromboembolic disease, pulmonary fibrosis, obliterative bronchiolitis, and

lymphangioleiomyomatosis"; and the term "antiproliferative agent" as "an agent having antiproliferative effects on vascular sooth muscle cells and endothelia cells".

The interpretation of the instant claims allows for the inclusion of treatment of various diseases not only proliferative and oliterative vascular diseases of lung including primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, pulmonary fibrosis, obliterative bronchiolitis, and lymphangioleiomyomatosis, but also diseases associated with thromboembolic diseases including stroke, coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, cerebral thromboembolism, arteriovenous fistula, atheroembolism and etc..., comprising administering any agent having antiproliferative effects on vascular smooth muscle cells and endothelial cells.

With respect to the scope of enablement for "a lung proliferative vascular disorder", "chronic thromboembolic disease", "an antiproliferative agent" or "an additional active agent",

The relative skill of the artisan and the unpredictability of the pharmaceutical art is very high. To practice the instant invention to the claimed scope, applicant would have to (i) screen numerous possible compounds characterized as "an antiproliferative agent" or "an additional active agent", (ii) assay to find out which compounds are able to possess antiproliferative effects on vascular sooth muscle cells and endothelia cells at what concentration level and then (iii) extrapolate the test and result to the claimed invention. In other words, the instant invention

necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the examples provided in the instant to the larger and highly varied genera of compounds that are "an antiproliferative agent" or "an additional active agent", without undue amount of experimentation.

As discussed above, the scope of the instant claims encompasses treatment of multiple complex disorders that may have unrelated manifestations including primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, pulmonary fibrosis, obliterative bronchiolitis, lymphangioleiomyomatosis, coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism and etc...

The instant specification provides assays to test simvastatin in vivo and discloses that said compound exhibit efficacy in decreasing pulmonary arterial hypertension, pulmonary artery neointimal formation and right ventricular hypertrophy (Examples). However, there is no

demonstrated correlation that the tests and results apply to all of the diseases or disorders embraced by the instant claims.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed "hepatotoxic compound" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-10, 12-13 and 19-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that the HMG-CoA reductase inhibitor is present in amounts "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient". The specification does not provide a standard for

ascertaining the requisite degree of "does not substantially increase...", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant is requested to clarify.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-7, 19-22, 30-31, 33-36 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Nishimura et al. (American Journal of Respiratory and Critical Care Medicine, Vol. 166, 2002, pp. 1403-1408).

Nishimura teaches the use of HMG-CoA reductase inhibitor such as simvastatin in attenuating vacular remodeling with neointimal formation, pulmonary arterial hypertension, right ventricular hypertrophy, decreasing neointmal vascular occlusion and improving blood flow in the systemic arterial circulation in rat study, wherein the simvastatin is administered in 2mg/kg daily by oral gavage; and wherein lung endothelia nitric oxide synthase gene expression is restored toward normal levels in simvastatin-treated animals (abstract; results; discussions).

With respect to the activity of simvastatin in "does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient" (claim 1) and "the blood flow is increased by from about 5% to at least about 300%" (claim 21), such properties or characteristics deems to be inherent to the referenced method since the

administration of same compound (i.e., simvastatin) in overlapping dosage amount inherently possessing therapeutic effect for the same ultimate use as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

9. Claims 1-10, 12, 19-22, 30-36 and 38-9are rejected under 35 U.S.C. 102(b) as being anticipated by Liao et al. (WO 00/56403).

Liao teaches the use of HMG-CoA reductase inhibitor such as simvastatin in treating pulmonary arterial hypertension or thromboembolism or increasing blood flow in tissue of a subject alone (page 13, line 19 thru page 14, line 1; page 16, line 2 thru page 17, line 7) or in combination with other active agent such as prostaglandin (page 24, line 16), wherein the simvastatin is administered in 0.01 mg/kg per day to 1000 mg/kg per day (page 10, lines 5-8), in various dosage forms including oral, rectal, topical, nasal, interdermal or patenteral (page 21, lines 3-11.

With respect to the activity of simvastatin in "does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient" (claim 1), "neointimal smooth muscle cell hyperplasia is decreased" (claim 19), "the blood flow is increased by from about 5% to at least aboue 300%" (claim 21) or "reversing right ventricular hypertrophy" (claim 30), such properties or characteristics deems to be inherent to the referenced method since the administration of same compound (i.e., simvastatin) in overlapping dosage amount inherently possessing therapeutic effect for the same ultimate use as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 23-24 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liao et al. (WO 00/56403) or Nishimura et al. (American Journal of Respiratory and Critical Care Medicine, Vol. 166, 2002, pp. 1403-1408).

The teaching of Liao or Nishimura has been discussed in above 35 USC 102(a) or (b) rejection.

Liao or Nishimura differs from the claimed invention in inhalation administration, particularly powder inhaler, metered dose inhaler or nebulizer.

However, those of ordinary skill in the art would have been readily optimized effective delivery forms as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate delivery dosage forms for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the conventional drug delivery forms known in pulmonary hypertension treatment of art.

11. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liao et al. (WO 00/56403).

The teaching of Liao has been discussed in above 35 USC 102(b) rejection.

The teaching of Liao differs from the claimed invention in the selection of prostacyclin. However, one having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that prostacyclin would not significantly alter the analogous properties of the compound of the reference due to close similarity of the compounds.

Conclusion

12. No Claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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